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Chapter 5

NICKEL TOXICITY

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INTRODUCTION

The first reported investigation of the toxic effects of nickel was published in 1826 by Gmelin, who found that the administration of large doses of nickel sulfate to rabbits and dogs by stomach tube resulted in severe gastritis and fatal convulsions and that a sublethal dosage of nickel sulfate by gavage produced cachexia and conjunctivitis. In the 150 yr following this report, numerous descriptions of the toxic effects of nickel have appeared. In recent years there have been several reviews on the subject. In this chapter the most pertinent material discussed in the excellent and comprehensive review by Sunderman et al. (1975) will be summarized and updated. Since a chapter on metal carcinogenesis appears elsewhere in this volume, nickel carcinogenesis will not be discussed here.

Nickel enters the body by four different routes—oral intake, inhalation, parenteral administration, and percutaneous absorption. The signs of nickel toxicity, the mechanisms behind the toxicological action of nickel, and the therapeutic measures to counteract nickel toxicity for these four routes of entry will be discussed.

NICKEL TOXICITY THROUGH ORAL INTAKE

The toxicity of nickel, or nickel salts, through oral intake is low, ranking with such elements as zinc, chromium, and manganese. Nickel salts exert their action mainly by gastrointestinal irritation and not by inherent toxicity (Schroeder et al., 1961). The basis for the relative nontoxicity of nickel appears to be a mechanism in mammals that limits intestinal absorption of nickel. In addition, nickel has little tendency to accumulate in tissues during lifetime exposure.

Large doses of oral nickel salts are necessary to overcome the homeostatic control of nickel. Nickel carbonate, nickel soaps, and nickel catalyst supplemented in the diet of young rats at 250, 500, and 1,000 μg/g for 8 wk, or nickel catalyst supplemented in the diet at 250 μg/g for 16 months, had no effect on the general condition or growth rate (Phatak and Patwardhan, 1950, 1952). These high levels of dietary nickel did result in higher tissue nickel contents. The highest concentration (140–360 μg/g) was found in bone. Other tissues contained 10–50 μg nickel/g.

Nickel acetate and nickel chloride may be somewhat more toxic to rats than the aforementioned materials. Whanger (1973) found that feeding 500 μg nickel acetate/g diet to weanling rats for 6 wk significantly depressed growth. High dietary levels of nickel acetate (500–1,000 μg/g) also significantly depressed hemoglobin concentrations, packed cell volumes, plasma alkaline phosphatase activity, and heart cytochrome oxidase activity. Other findings were increased nickel, iron, and zinc content in both plasma and red blood cells, increased nickel content in heart, liver, testes, and kidney (levels of 2–40 μg nickel/g tissue were found), and a two- to threefold increase in iron content in some of these tissues. Nickel accumulated in the soluble fraction of the liver and in the soluble fraction, nuclei, and debris of the kidney. An accumulation of iron occurred in all of the cellular fractions of these two tissues.

Clary (1975) found that feeding 225 μg nickel chloride/ml drinking water for 4 months was toxic to rats. The signs of toxicity were depressed growth, lower serum triglyceride and cholesterol concentrations, and less total urine, urinary calcium, and urinary zinc. High levels of nickel sulfate (25 mg/kg daily) orally administered to male rats for 120 days resulted in marked dystrophic histological changes in the testes, and the activities of succinic dehydrogenase, DPN-diaphorase and steroid-3β-dehydrogenase were depressed in this organ (Vulcheva et al., 1970).

Schroeder et al. (1974) and Schroeder and Nason (1974) found a much lower level of dietary soluble nickel (5 μg/ml drinking water) fed to rats of both sexes for life to be virtually innocuous, not affecting survival, longevity, incidence of tumors, or specific lesions. Feeding this level of nickel was associated with increased concentrations of chromium in heart and spleen and of manganese in kidney and decreased concentrations of copper in lung and spleen, zinc in lung, and manganese in spleen. Nickel did not accumulate in any tissue examined. Schroeder and Mitchener (1971) reported that a similar exposure of soluble nickel in drinking water to breeding rats may be moderately toxic during reproduction. When carried through three generations, 5 μg nickel/ml drinking water apparently caused increased perinatal death and the occurrence of runting. The size of the litters decreased with each generation, and few males were born in the third generation.

Nickel is apparently less toxic to mice than to rats. Weber and Reid (1969) found that 1,100 μg nickel/g diet in the form of nickel acetate

depressed the growth of female mice, but 1,600 μg nickel/g diet was needed to reduce growth in males. Dietary nickel at the 1,100 μg/g level decreased the activities of liver cytochrome oxidase and isocitric dehydroganse. At the 1,600 μg/g level the following enzyme activities were depressed: liver NADH-cytochrome *c* reductase, heart cytochrome oxidase, and malic dehydrogenase and kidney malic dehydrogenase. These investigators also observed that these high levels of dietary nickel had no influence on body weights of adult mice; if these mice were allowed to breed, however, 1,600 μg/g dietary nickel significantly reduced the number of pups weaned per litter. Dietary nickel at 1,100 μg/g had no effect on reproduction, which is in contrast to the observations on rats reported by Schroeder and Mitchener (1971). Mice tolerate low levels of nickel acetate in their drinking water (5 μg nickel/ml) over their lifetime without apparent difficulty. In terms of growth, survival, and tumor incidence, nickel administered in this manner was essentially inert (Schroeder et al., 1963, 1964).

Nickel chloride administered orally to young male rabbits at 500 μg/day for 5 months resulted in decreased liver glycogen, increased muscle glycogen, and a prolonged hyperglycemia after a glucose load (Gordynya, 1969). Oral administration of 0.2 or 0.5 mg nickel sulfate/day for 150 days resulted in a dose-dependent increase in nickel in all organs and tissues of rabbits, with the highest increase observed in liver and muscle (Moiseeva, 1973).

When chicks were fed diets containing nickel, as either the sulfate or the acetate, a significant decrease in growth was observed at a level of 700 μg/g or above (Weber and Reid, 1968). Up to 300 μg/g the body weights were normal. Nitrogen retention decreased progressively above 500 μg/g. The higher dosages of nickel that caused growth depression also reduced food consumption. Thus when food consumption was equalized by pair feeding, 1,100 μg/g dietary nickel did not affect growth, although nitrogen retention was decreased.

O'Dell et al. (1970b, 1971b) studied nickel toxicity in young bovines employing four levels of supplemental dietary nickel: 0, 62.5, 250, and 1,000 μg/g as nickel carbonate. The signs of toxicity were similar to those for chicks. Feed intake and growth were slightly retarded by 250 μg nickel/g diet. At the dietary level of 1,000 μg/g feed intake and growth were greatly reduced. The calves, however, were not emaciated, but did appear to be younger than the calves fed the lower levels of supplemented nickel. The kidneys of the experimental animals were nephritic, and the degree of severity increased with nickel toxicity. The high dietary level of nickel lowered nitrogen retention and caused anorexia. The 1,000 μg/g dietary nickel also resulted in an increased nickel content in many tissues, with the exception of the liver and heart. The increase in tissue nickel concentration occurred even though food intake was reduced; thus the total nickel intake was not much greater than when the diet was supplemented with 250 μg nickel/g. Apparently, 1,000 μg nickel/g diet will overwhelm homeostatic control mechanisms.

In other experiments O'Dell et al. (1970a) found that nickel chloride was more toxic to calves than was nickel carbonate. They also found that either 100 μg nickel/g as the chloride or 500 μg nickel/g as the carbonate reduced the palatability of the diet for calves, but did not do so at half these amounts. Feeding lactating dairy cows 250 μg nickel/g concentrate ration had no significant effect on milk production, milk composition, animal health, or feed consumption (O'Dell et al., 1971a). Milk from the cows contained less than 0.1 μg nickel/ml.

Diets containing nickel at 250, 500, and 1,000 μg/g as nickel catalyst, nickel soap, and nickel carbonate were innocuous when fed to monkeys for 24 wk as judged by growth, behavior, hemoglobin concentration, red cell count, and white cell count (Phatak and Patwardhan, 1950). Nickel content of tissues or organ histopathology was not examined.

It appears that many of the signs of nickel toxicity are the result of reduced food intake, partially caused by reduced palatability. However, homeostatic mechanisms controlling nickel absorption and excretion can be disrupted, thus increasing the tissue levels of nickel. Since nickel is a divalent cation, it reacts with active groups on proteins. Such reactions might explain the findings of reduced tissue enzyme activities in animals fed high levels of nickel.

The chances of nickel toxicity occurring under usual circumstances by the oral route are remote given the large amount of nickel required to produce toxic effects by ingestion. However, if it does occur, an appropriate therapeutic measure is the reduction or elimination of the unnatural source of nickel.

NICKEL TOXICITY VIA PARENTERAL ADMINISTRATION

In contrast to nickel salts administered orally, nickel salts administered intravenously or subcutaneously are highly toxic. Most available data on parenteral LD_{50} for various nickel compounds have been tabulated (Sunderman et al., 1975). The LD_{50} ranges from 6 mg nickel oxide/kg given intravenously to dogs to 600 mg nickel disodium EDTA/kg administered intraperitoneally to mice. Gross signs of nickel toxicity as a result of parenterally administered nickel salts include gastroenteritis, tremor, convulsions, paralysis, coma, anaphylactoid edema, and death.

Sublethal, but toxic doses, of parenterally administered nickel salts had effects on several biochemical parameters. Subacute injection of nickel L-glutamate increased total lipids, phosphatides, free fatty acids, and cholesterol in the serum or plasma of rabbits (Fiedler and Hoffmann, (1970). Subacute injection of nickel chloride (5 mg nickel/kg) into rabbits inhibited ADP-induced platelet aggregation in plasma samples taken 4 and 24 hr postinjection (Fiedler and Herrmann, 1971). This effect was correlated with a parallel increase in plasma lipids. Joó (1968, 1969) found that 0.01, 0.015, or

0.25 g/kg nickel chloride given intravenously changed the molecular organization of the basement membrane in rat brain capillaries. Structural looseness and finger-like hypertrophy occurred. This was followed by various degrees of formation of collagen-like fibers in the substance of the basement membrane. At the time these changes occurred, he found that nickel chloride specifically inhibited ATPase activity in the capillary walls. Joó suggested that the inhibition of ATPase was the primary cause of the changes in the blood brain barrier.

Intravenous injection of nickel chloride into cats resulted in severe disturbances of heart excitability, conductivity, and automatism, and decreased Ca^{2+} and K^{+} in the right atrium and Ca^{2+} in the left ventricle (Malyshev, 1971).

Parenterally administered nickel also affects glucose metabolism. Freeman and Langslow (1973) found that intraperitoneal nickel chloride (10 mg/kg) in chicks resulted in a transient but significant increase in plasma glucose after 15 min followed by a progressive fall to the hypoglycemic range 60 and 120 min postinjection. In chicks starved 16 hr prior to injection, a hyperglycemic response occurred within 15 min, which persisted throughout the 2-hr experimental period. Clary (1975) reported that a single intraperitoneal or intratracheal injection of nickel chloride to rats caused a rapid transient increase in serum glucose, a decrease in serum insulin, and glucosuria. When exogenous insulin was given simultaneously with the nickel challenge, the increase in serum glucose was prevented. Glucose turnover studies revealed that the effect of nickel appeared to be an inhibition of insulin release by the pancreas. High concentrations of nickel were found in the pituitary gland. Therefore it was suggested that the inhibition of insulin release was related to a secretion of certain pituitary hormones—growth hormone and adrenocorticotropin—in response to nickel. Support for this hypothesis was provided by *in vitro* studies of LaBella et al. (1973a). They found that nickel increased the rate of release of growth hormone and adrenocorticotropin and decreased the rate of release of prolactin by the pituitary. LaBella et al. (1973b) also reported that intravenous administration of nickel chloride (300–600 μg/kg) to chlorpromazine-treated male rats resulted in a 40% decrease in serum prolactin 30 min postinjection. This finding suggests a direct, specific inhibitory action of nickel on prolactin-secreting cells of the anterior pituitary.

Dormer et al. (1973) reported that nickel inhibited the release of amylase from rat parotids, insulin from mouse pancreatic islets, and growth hormone from bovine pituitary slices when release was evoked by a variety of stimuli both physiological and pharmacological. They suggested that nickel might have blocked exocytosis by interfering with secretory granule migration or membrane fusion and microvillus formation. An antagonism between nickel and calcium ions in stimulus-secretion coupling might also have been in part responsible.

Jasmin (1974) found that injections of nickel sulfide, chloride, or sulfate

induced anaphylactoid edema in rats. Intraperitoneally or intravenously injected nickel salts (5 mg/100 g) evoked erythema and exoserosis within 1–10 min. Mast cells in the subcutaneous tissue of edematous ear lobes were often degranulated. Since it appears that nickel does not directly induce histamine release from, or degranulation of, mast cells (Taubman and Malnick, 1975), it has been suggested that nickel complexes with a preexisting protein to give a substance capable of mast cell degranulation.

Possible mechanisms of action of parenteral nickel were suggested previously, They include enzyme inhibition (ATPase) that might cause neurological abnormalities including tremor, convulsions, and coma; inhibition or stimulation of hormone release or action; internal rearrangement of Ca^{2+} ions in muscle that might cause paralysis and abnormal heart rhythm; and indirect stimulation of mast cell degranulation that might result in anaphylactoid edema.

Nickel toxicity induced through parenteral intake occurs only under experimental conditions. Thus there has been essentially no investigation into the therapeutic measures to be used in this type of toxicity. Injected nickel is rapidly cleared from plasma or serum (Onkelinx et al., 1973). Thus if the animal survives the initial toxic effect of the nickel salt, it will recover within a few days.

Two means of parenteral nickel administration have not been discussed in this section. The injection of nickel carbonyl gives results similar to those caused by its inhalation (Hackett and Sunderman, 1967). This will be discussed in the inhalation toxicity section. Nickel introduced in the body via metallic devices and prostheses may result in dermatological responses. This toxic response is similar to that observed with the percutaneous administration of nickel to sensitive individuals and will be discussed in the section on percutaneous absorption.

NICKEL TOXICITY CAUSED BY PERCUTANEOUS ABSORPTION

For more than 60 yr it has been known that contact with nickel, or with solutions of nickel salts, can result in dermatitis. Herxheimer described nickel dermatitis in industrial workers in 1912. The prevalence of nickel dermatitis in modern society has been reviewed (Sunderman et al., 1975). Nickel allergy, an important problem in everyday life, has the highest incidence among women. The first described cases of nickel dermatitis were observed in nickel miners, smelters, and refiners and was termed "nickel itch." The clinical manifestations including an itching or burning papular erythema in the web of the fingers, which spread to the fingers, the wrists, and the forearms. Nickel dermatitis is usually papular or papulovesicular and has characteristics similar to those of atopic dermatitis, rather than of eczematous contact dermatitis.

Baer et al. (1973) reported that the incidence of allergic contact

sensitivity to nickel, as determined by reaction to nickel sulfate on selected patient populations, has been quite constant over a period of 33 yr (1937–1970)—approximately 12%. In other surveys (Sunderman et al., 1975) the percentage of nickel reactivity ranged from 4 to 13%. These data indicate that a large number of persons are sensitive to cutaneously applied nickel.

Occupational sources of exposure to nickel include nickel mining, extraction and refining, plating, casting, grinding and polishing, nickel powder metallurgy, nickel alloys and nickel-cadmium batteries, chemical industry, electronics and computers, food processing, and nickel waste disposal and recycling (Sunderman et al., 1975). Persons in other occupations in which they may contact nickel include nickel catalyst makers, ceramic makers and workers, duplicating-machine workers, dyers, ink makers, jewelers, spark plug makers, and rubber workers.

Due to technological improvements and advances, nickel dermatitis is seen infrequently in major industries. However, it still is a problem in electroplating shops (Kadlec, 1969).

There are many sources of contact with nickel for persons who are sensitive to this metal. These include jewelry, coins, clothing fasteners, tools, cooking utensils, stainless steel kitchens and kitchenware, detergents, prostheses, and other medical appliances. That such sources of exposure to nickel can cause dermatitis was shown by Fisher and Shapiro (1956). Among the sources of nickel they reported as causing dermatitis were earrings, garter clasps, metal chairs, thimbles, needles, scissors, nickel coins, fountain pens, car door handles, necklace clasps, zippers, watch bands, bracelets, bobby pins, spectacle frames, safety pins, shoe eyelets, metal arch supports, eyelash curlers, and handbags. They found that they could patch test for nickel sensitivity by using nickel coins. Rostenberg and Perkins (1951) reported an individual who reacted to wearing a jacket having metal clasps. Stoddart (1960) reported two case studies of patients who reacted to nickel cannulae used for routine intravenous infusions. Tinckler (1972) reported a case of skin sensitivity to surgical skin clips. Reports of "internal" allergic contact dermatitis caused by nickel-containing prostheses have also been published (McKenzie et al., 1967; Barranco and Soloman, 1972).

The mechanism of sensitization for nickel is probably similar to that of other simple chemicals. That is, nickel ions contact the surface of the skin, penetrate the epidermis, and combine with a body protein. The body then reacts to this conjugated protein. It has been suggested that in all likelihood, the specificity of the reaction is determined primarily by the haptenic portion of the molecule, nickel; however, the carrier protein necessary to make the complex antigen need not be inert and may be the immunologic determinant (Sunderman et al., 1975). Several studies have shown that nickel ions can be leached from household and everyday items, medical equipment, and prostheses (Ferguson et al., 1962; Mears, 1966; Samitz and Klein, 1973; Katz and Samitz, 1975; Samitz and Katz, 1975) by physiological saline, blood, sweat,

and other body fluids. Wells (1956) reported that nickel ions can penetrate the skin via the sweat ducts and hair-follicle ostia and that they have a special affinity for keratin. Based on histochemical evidence, Wells suggested that nickel is bound by the carboxyl groups of keratin. Kolpakov (1963), using cadaver skin as an experimental model, found the malpighian layer of the epidermis, the dermis, and the hypodermis were readily permeable to nickel sulfate. The greatest accumulation of nickel was found in the malpighian layer, the sweat glands, and the walls of the blood vessels. The stratum corneum was a barrier to the penetration of nickel sulfate. Spruit et al. (1965), also using cadaver skin, reported that nickel ions penetrate and are bound by the dermis. He suggested nickel bound by the dermis can serve as a reservoir for subsequent release of nickel ions. Since nickel is an ion of the first transition series, it is not unexpected that it would bind to a variety of proteins. Evidence for binding of nickel to albumin, lysine vasopressin, conalbumin, alpha-chymotrypsin, ribonuclease, myoglobin, pseudoglobin, and keratin has been reported (Cotton, 1964; Bryce et al., 1966; Tsangaris et al., 1968; Callan and Sunderman, 1973). Recent evidence has shown that nickel might participate in a latter step of the series of reactions necessary for the interaction of guinea pig complement with immune aggregate (Amiraian et al., 1974).

Once the diagnosis of nickel contact dermatitis has been established, removal of the patient from the source of nickel contact should be followed by the alleviation of the malady. Prevention of further dermatitis requires prevention of contact with nickel-containing items. Cloth or plastic substitutes should be used. Some protection may be given by introducing a physical barrier between the skin and the metal. Fingernail polish, lacquer (Fisher, 1967), or polyurethane coating (Moseley and Allen, 1971) has been used for such a barrier. Fisher (1964) reported that a film formed by spraying the skin with topical aerosol dexamethasone was effective in preventing nickel dermatitis. Kurtin and Orentreich (1954) reported an active chelating agent (such as disodium EDTA) applied in ointment form will inhibit the appearance of a positive nickel patch test applied over the ointment site.

NICKEL TOXICITY CAUSED BY INHALATION

Because of its industrial importance, nickel carbonyl toxicity has been extensively studied. Nickel carbonyl is a colorless, volatile liquid (boiling point 43°C) that is particularly dangerous if inhaled. A variety of pathological lesions can result from the inhalation of nickel carbonyl, depending on amount inhaled and the duration of exposure. Chronic exposure to nickel carbonyl (and respirable particles of nickel, nickel subsulfide, and nickel oxide) can cause cancer. This was reviewed (Sunderman et al., 1975) recently and is also discussed elsewhere in this volume. Signs and symptoms that occur in animals following acute exposure to nickel carbonyl include dyspnea,

tachypnea, cyanosis, fever, apathy, anorexia, vomiting, diarrhea, and, occasionally, hind limb paralysis. Generalized convulsions are frequently a terminal event. The pathological lesions following experimental acute exposure in animals are summarized in Table 1. In lung (the primary target organ for nickel carbonyl) findings include edema, focal hemorrhage, capillary congestion, alveolar cell degeneration, inflammation, and interstitial fibrosis. The lesions in other organs are less severe than those in the lung. They include edema, congestion, focal hemorrhage, hydropic degeneration, inflammation, and vacuolization in such organs as adrenals, brain, kidney, liver, pancreas, or spleen. If death occurs, it usually happens between the third and fifth day after exposure.

The clinical manifestations of nickel carbonyl poisoning in 25 men and the relative occurrence of the symptoms and signs are shown in Table 2. Other symptoms and signs observed in human nickel carbonyl poisoning (Sunderman, 1970) include cough, hypernea, cyanosis, leukocytosis, and increased temperature and pulse rate. Terminally, patients frequently become delirious. Tseretili and Mandzhavidze (1969) reported hyperglycemia, glucosuria, and heptomegaly in patients with severe nickel carbonyl poisoning. The pathological findings in men who died from nickel carbonyl inhalation were similar to those of experimental animals (Sunderman et al., 1975). In humans death usually occurs 3–13 days after exposure and is attributed primarily to respiratory failure. Cerebral edema and punctate cerebral hemorrhages might also be contributing causes of death. Patients who recover from nickel carbonyl poisoning often have a long period of convalescence (see Table 2) during which time they fatigue easily.

Very small amounts of nickel carbonyl were required to produce the toxic manifestations in animals (Table 1). Armit (1908) found that inhaled nickel carbonyl is approximately 100 times more toxic than carbon monoxide. A lethal atmospheric concentration of nickel carbonyl for a man is 30 μg/ml for a 30-min exposure (Kincaid et al., 1956).

Inhaled or injected nickel carbonyl does not immediately decompose and can pass across the alveolar membrane in either direction without metabolic alteration (Sunderman et al., 1968; Sunderman and Selin, 1968; Kasprzak and Sunderman, 1969). Hackett and Sunderman (1967, 1968) and Sunderman and Selin (1968) suggested that pathological lesions in the lungs result from damage produced during transit of the nickel carbonyl across the alveolar epithelium. Sunderman, Jr. (1971) also proposed that acute toxicity of nickel carbonyl might be partly due to an inhibition of ATP utilization.

On the basis of clinical experience, sodium diethyldithiocarbamate (Dithiocarb) is currently the drug of choice for the treatment of nickel carbonyl poisoning (Sunderman and Sunderman, 1958; Sunderman, 1964, 1971). After the initiation of oral Dithiocarb therapy, the urinary excretion of nickel is promptly increased, and the clinical manifestations of nickel carbonyl poisoning are relieved in a few hours. With continued Dithiocarb therapy, the

TABLE 1 Pathologic Lesions after Acute Exposure of Experimental Animals to Nickel Carbonyl[a]

Authors	Route of administration	Animal	Dose	Observation period after exposure	Observations
Armit, 1908	Inhalation	Rabbit	1.4 mg/liter for 50 min	1–5 days	*Lungs:* intraalveolar hemorrhage, edema, and exudate and alveolar cell degeneration; *adrenals:* hemorrhages; *brain:* perivascular leukocytosis and neuronal degeneration
Barnes and Denz, 1951	Inhalation	Rat	0.9 mg/liter for 30 min	2 hr to 1 yr	*Lungs:* at 2–12 hr capillary congestion and interstitial edema; at 1–3 days massive intraalveolar edema; at 4–10 days pulmonary consolidation and interstitial fibrosis
Kincaid et al., 1953	Inhalation	Rat	0.24 mg/liter for 30 min	0.2 hr to 6 days	*Lungs:* at 1 hr pulmonary congestion and edema; at 12 hr to 6 days interstitial pneumonitis with focal atelectasis and necrosis, and peribronchial congestion; *liver, spleen, kidneys, and pancreas:* parenchymal cellular degeneration with focal necrosis
Sunderman et al., 1961	Inhalation	Rat Dog	1.0 mg/liter for 30 min	1–6 days 1–7 days	*Lungs:* at 1–2 days intraalveolar edema and swelling of alveolar lining cells; at 3–5 days inflammation, atelectasis, and interstitial fibroblastic proliferation; *kidneys and adrenals:* hyperemia and hemorrhage
Hackett and Sunderman, 1967	Intravenous	Rat	65 mg/kg	0.1 hr to 21 days	*Lungs:* at 1–4 hr perivascular edema; at 2–5 days severe pneumonitis with intraalveolar edema, hemorrhage, subpleural consolidation, hypertrophy and hyperplasia of alveolar lining cells, and focal adenomatous proliferation; at 8 days interstitial fibroblastic proliferation; *liver, kidneys, and adrenals:* congestion, vacuolization, and edema

Hackett and Sunderman, 1968	Intravenous	Rat	65 mg/kg	0.5 hr to 8 days	*Lungs:* ultrastructural alterations, including edema of endothelial cells at 6 hr and massive hypertrophy of membranous and granular pneumocytes at 2–6 days
Hackett and Sunderman, 1969	Intravenous	Rat	65 mg/kg	0.5 hr to 6 days	*Liver:* ultrastructural alterations of hepatocytes including nucleolar distortions at 2–24 hr, dilatation of rough endoplasmic reticulum at 1–4 days, and cytoplasmic inclusion bodies at 4–6 days

[a] As tabulated by Sunderman et al. (1975).

TABLE 2 Clinical Manifestations of Nickel Carbonyl Poisoning in 25 Men[a]

Immediate symptoms	Dyspnea (80%), fatigue (80%), nausea (76%), vertigo (44%), headache (36%), odor of "soot" in exhaled breath (36%), vomiting (24%), and insomnia and irritability (24%)
Latent period	In half of subjects, an asymptomatic interval between recovery from initial symptoms and onset of delayed symptoms
Delayed symptoms	Dyspnea with painful inspiration (80%), nonproductive cough (64%), muscular weakness (44%), substernal pain (44%), chilling sensations (32%), muscular pain (28%), sweating (24%), visual disturbances (12%), diarrhea (12%), abdominal pain (4%), muscle cramps (4%), and hypoesthesia in legs (4%)
Physical and X-ray findings	Tachypnea and tachycardia (80%), interstitial pneumonitis on X-rays (60%), fever (40%), and cyanosis (36%)
Laboratory findings	Pulmonary function tests consistent with interstitial lung disease (40%), increased serum glutamic pyruvic transaminase (36%), increased serum glutamic oxaloacetic transaminase (32%), and low arterial pO_2 (32%)
Clinical course	Interval before hospitalization: median, 2 days; range, 0–7 days. Duration of hospitalization: median, 6 days; range, 0–27 days. Interval before recovery: median, 38 days; range, 1–88 days. Symptoms that persisted for more than 3 wk: fatigue (88%), exertional dyspnea (52%), muscular weakness (48%), headache (36%), abdominal pain (36%), muscular pain (32%), sweating (24%), visual disturbances (16%), and muscle cramps (8%)

[a]From Sunderman et al. (1975). Based on observations of Vuopala et al. (1970).

patients show uneventful recoveries. Sunderman (1971) reported that there were no deaths among 50 men with acute nickel carbonyl poisoning and that all returned to work within 3 wk following treatment with Dithiocarb. In comparison, of 31 acute nickel carbonyl-poisoned patients treated with dimercaprol (Sunderman and Kincaid, 1954), two died, and the period of convalescence for most of the others lasted several months.

Sunderman (1971) recommended the following therapeutic regimen for patients with known or suspected acute nickel carbonyl poisoning.

1. In cases where the extent or severity of exposure is unknown, give 0.2 g Dithiocarb and 0.2 g sodium bicarbonate with water every 2 min until 2 g Dithiocarb has been given. The divided doses and sodium bicarbonate are required to prevent nausea. If the symptoms of nickel carbonyl poisoning are minimal, further therapy

considerations may be deferred until the nickel content of the urine is known.

2. In mild cases (initial 8-hr specimen of urine contains less than 10 μg nickel/100 ml), it is probable that delayed symptoms will not develop or will be minimal. No therapy is required; however, an occasional patient may complain of fatigue and require rest. If severe delayed symptoms develop unexpectedly, the patient should be hospitalized and treated the same as patients with moderately severe nickel carbonyl poisoning.
3. In moderately severe cases (initial 8-hr specimen of urine contains 10-50 μg nickel/100 ml) a dosage of 25 mg Dithiocarb/lb body weight should be administered the first day. For example, a 160-lb man should receive an initial 2 g (in divided doses with sodium bicarbonate as described in 1, above); 4 hr later another gram; 0.6 g at the eighth hour; and 0.4 g 16 hr after exposure. Dithiocarb therapy should continue at a dosage of 0.4 g every 8 hr until the patient is free of symptoms and the urine nickel content is normal. The patient should be under close observation for at least 1 wk as delayed poisoning symptoms may develop.
4. In severe cases (initial 8-hr specimen of urine contains greater than 50 μg nickel/100 ml), patients are usually quite ill and require hospitalization. Unless the clinical condition is critical, the patient may be treated in the same way as the moderately severely poisoned patient. Parenterally administered Dithiocarb (12.5 mg/lb body weight) is suggested for critical cases. Further dosage is governed by clinical evaluation. The total amount given in the first 24 hr after exposure may be increased to as much as 50 mg/lb body weight.

Patients receiving Dithiocarb should abstain from alcoholic beverages for 1 wk following therapy or they may experience symptoms similar to those observed in people who ingest alcohol after an antabuse treatment. Sedatives, such as paraldehyde and chloral hydrate, tranquilizers, and other psychopharmacologic drugs are contraindicated during Dithiocarb therapy.

Studies of the effects of inhalation of nickel compounds other than nickel carbonyl are limited. Bingham et al. (1972) observed that rats exposed to an aerosol of nickel oxide exhibited an increased number of alveolar macrophages. They also noted a marked increase in mucus in rats exposed to an aerosol of nickel chloride. Both nickel compounds produced lung changes that were visible with the light microscope. After long exposure of the rats to nickel oxide, some thickening of the alveolar walls was visible. Inhalation of nickel chloride resulted in hyperplastic bronchial epithelium. Eliseev (1975) reported that rats inhaling 0.005-0.5 mg nickel chloride/m^3 air for 6 months showed suppressed iodine binding activity of the thyroid gland. Nickel

introduced via the respiratory route had a greater inhibiting effect on the thyroid than nickel administered orally.

McConnell et al. (1973) reported a case of asthma associated with the inhalation of nickel sulfate. The patient, who worked in a nickel-plating company, also had nickel dermatitis. Immunologic studies showed circulating antibodies to the nickel salt; controlled inhalation exposure to a solution of nickel sulfate reproduced the illness. In cases of nickel toxicity of this type, the best therapy is removal from the source of nickel.

SUMMARY AND CONCLUSIONS

Nickel can be a toxic element. The toxicological manifestations of nickel depend on the form, level of exposure, and mode of entry into the body. Nickel or nickel salts are relatively nontoxic when taken orally. Abnormally high levels of dietary nickel are required to overcome homeostatic mechanisms that control nickel metabolism. Nickel toxicity in humans via the oral route occurs only in extreme and unusual circumstances. Nickel toxicity from parenteral administration has been observed only under experimental conditions and, therefore, is not a practical consideration for man. Nickel toxicity manifested by nickel dermatitis is relatively common. Since many items in everyday use contain nickel, this type of nickel toxicity will always be present unless new and better methods of prevention and therapy are found. The most serious type of nickel toxicity is that caused by the inhalation of nickel carbonyl. Fortunately, the general population is not exposed to air containing this compound; acute nickel carbonyl poisoning usually occurs as a consequence of an industrial accident.

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